The Genesis of the Neuroendocrine Tumors Concept: From Oberndorfer to 2018

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KEYWORDS

• NET • Biomarker • Imaging • Somatostatin analogues • Chemotherapy • PRRT • Targeted agents

KEY POINTS

- Immunohistochemistry with specific antibodies for recognizing the neuroendocrine phenotype was introduced in the 1970s and 80s (chromogranin A, synaptophysin).
- The World Health Organization classification system established in 2000 was upgraded in 2004; 2010; and, finally, in 2017.
- Ki-67 was instituted as a reliable proliferation marker for neuroendocrine tumors (NETs) during the last decades.
- Plasma chromogranin A was confirmed as a general tumor marker over the past decades.
- Somatostatin analogues were developed in the early 1980s and have remained as the main therapy for treatment of hormone-related syndromes in NETs.

INTRODUCTION

The concept of neuroendocrine tumors (NETs) started to develop in the early 1900s with a description of carcinoid tumors by Oberndorfer[1] in 1907; followed by specific cytotoxic agents (streptozotocin); and, finally, the identification of somatostatin as a central regulator in neuroendocrine cell physiology but also an inhibitor of clinical symptoms related to NETs. The diagnosis of a NET was further confirmed by the World Health Organization (WHO) classification systems, which were introduced in 2000, and refined in 2010 and 2017. Histopathology now included immunohistochemistry with specific antibodies and chromogranin A was established as a general marker for NETs, both in cytochemistry and in circulation, working as a biomarker. The imaging was further refined during the 1980s and 1990s with the introduction of molecular imaging, first with somatostatin receptor (SSTR) scintigraphy and later with PET using

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gallium (Ga) labeled radiochemicals. Somatostatin analogues were introduced in the early 1980s for treatment of patients with clinical symptoms related to NETs, such as carcinoid syndrome, and are still the leading agents for controlling clinical symptoms from NETs related to hormone production. New therapies were developed during the last 2 decades, including peptide receptor radiotherapy (PRRT) and targeted agents, and were evaluated in prospective randomized controlled trials. The combination of progress in diagnoses and treatment of NETs established the current concept of NETs. The increasing interest in these tumors, which were previously suggested to be rare, is shown in their increased incidence and prevalence. Friedrich Feyter[2] introduced the concept of the diffuse endocrine cell system, recognizing the regulatory system of internal control of various body functions. Between 1960 and 1970, the true NET-concept was established with the development of radioimmunoassays for peptides and hormones, and imaging with computerized tomography (CT) was introduced in clinics.

THE EARLY DAYS AND ATTEMPTS TO UNDERSTAND THE REGULATION OF ORGAN AND BODY FUNCTIONS

Based on research in the 1860s and 1870s, Ivan Pavlov[3–5] (1849–1936) introduced the concept of nervism in 1883. His work on dogs supported his theory that the nervous system plays a dominant role in the regulation of all body functions. As late as 1935, when endocrine cells were already detected and discussed, he wrote that the more developed the nervous system becomes in an animal, the more centralized it is, and the more its highest division acts as a director and distributor of all functions of the organism. Although revolutionary, Pavlov's[3–5] work was incomplete in his failure to recognize the effect of the endocrine system in the regulation of organs. William Bayliss (1860–1924) and Ernest Starling[6] (1866–1927), challenged the concept of nervism. In a series of experiments conducted on the small intestines of animals, they demonstrated that agents in the blood could be responsible for pancreatic secretion. Based on this observation by Bayliss and Starling[6] (1902), the concept of hormones and secretin stimulated an extensive research to find the cells responsible for releasing these chemical messengers. In 1867, Paul Langerhans (1847–1888), a German pathologist and physiologist, discovered a previously unrecognized clusters of pancreatic cells embedded within sheets of acinar cells.[7] Although Langerhans recognized these as novel structures, he did not identify their endocrine function. Édouard Laguesse (1861–1927), a French pathologist, studied these pancreatic cell clusters, postulated that they produce an internal secretion, and coined the term, islets of Langerhans. In 1922, 30 years later, Frederick Banting (1891–1941) and Charles Best[8] (1899–1978) discovered the secretion of the hormone called insulin from these islets.[9] Enterochromaffin (EC) cells in the gastric mucosa of rabbits and dogs were first described in 1870 by Rudolf Peter Heidenhain[10] (1834–1897). He noted that the cells contained acidophilic granules and, 2 years later, he identified small granular yellow staining cells on the surface of gastric glands that are now understood to be histamine-secreting EC-like (ECL) cells. In 1891, Adolphe Nikolas[11] (1861–1939) reported the wide distribution of EC cells throughout the gastrointestinal (GI) tract. In 1897, Nikolai Kulchitsky[12] (1856–1925) noted similar cells with granules with acidophilic properties in the crypts of Lieberkühn and intestinal mucosa of cats and dogs. He noticed that the cells had something to do with digestion. In 1906, Ciaccio[13] identified the same cell type in the GI tract of humans and coined the term EC cells. In 1914, André Gosset (1872–1944) and Pierre Masson[14] (1880–1959) described argentaffin silver staining of the cells and tumors developing from these cell systems, and